REMARKS

Claims 1, 2, 5-9 and 14-23 are pending in the application. Claims 1, 2, 7-9 and 18-23 are rejected. Claims 5, 6 and 14-17 have been withdrawn from consideration.

Upon entry of the Amendment, claims 5-6 and 14-23 will be canceled, claims 24-25 added, and claims 1, 2, 7-9 and 24-25 will be pending.

Support for the amendment of claims 1 and 9 to recite the amino acid corresponding to lysine 42 of mouse CaMKIIα may be found in the last paragraph of page 3 of the specification.

Support for the amendment of claim 2 to replace the word "corpus striatum" with "caudate-putamen" may be found (i) at page 19, lines 18-20, of the specification where the abbreviation "CPu" appears after the word "corpus striatum", (ii) the enclosed Declaration of Yoko Yamagata, and (iii) enclosed pages 795-801 of "Carpenter's Human Neuroanatomy".

Support for new claims 24 and 25 may be found in paragraphs F), G) and I) on page 4 of the specification.

No new matter has been added. Entry of the amendment is respectfully requested.

I. Rejection Under 35 U.S.C. §103

At page 2 of the office action, claims 1, 2, 7-9 and 18-23 are rejected as being unpatentable under 35 U.S.C. §103(a) over Elgersma (2002), Wang (2003), Hanson (1994) and Sutoo (2002).

The Examiner states that the rejection of claims 1, 2 and 7-9 has been maintained for the reasons first set forth in the office action dated July 9, 2009. The Examiner has extended the rejection to new claims 18-23, and notes that while these claims recite the specific amino acid that is modified (lysine), Hanson allegedly teaches modification of this residue.

The Examiner has stated that the "claimed knock-in animals are essentially disclosed by Wang et al with the exception of the phenotype limitation in claim 2" (page 5, office action dated July 9, 2009), that the use of the mutant of Hanson with the knock-

in animals of Wang or Elgersma would have been obvious, and that the skilled artisan would have been motivated to produce the claimed knock-in animals to further knowledge on the role of CaMKIIα in memory and learning. The Examiner concludes that "the totality of the prior art teaches the predictable generation of CaMKIIα mutants with the claimed activity."

Applicants respectfully traverse the Examiner's position for the reasons of record set forth in the Amendment filed November 9, 2009[1], and for the following additional reasons.

First, Applicants note that the scope of the claims has been narrowed herein to specify that the lysine residue in the catalytic domain of CaMKIIα (corresponding to Lys-42 of the mouse protein) is replaced by an arginine. Thus, the claimed knock-in animals and cells are those that have specific physical and physiological characteristics.

Second, Applicants respectfully assert that combination of the teachings provided in the documents would not have yielded predictable results to the skilled artisan. Indeed, the skilled artisan would not have had a reasonable expectation of success in producing a knockin animal having the claimed characteristics in light of the art cited by the Examiner and the knowledge of the skilled artisan. In particular, none of the documents cited by the Examiner would have suggested to the skilled artisan that a viable transgenic animal could be produced where the CaMKIIα protein had impaired kinase activity, yet retained both calmodulin binding activity and multimerizing activity. Hanson only studied the activity of mutated CaMKIIα protein transiently expressed in a cell line (COS cells), a cell line that does not naturally produce the protein, and the mutation was introduced at a cDNA level, but not at a genomic DNA level. Wang only provides the results of studies on the *overexpression* of an active form of the CaMKIIα protein in mice. While Wang also describes inactivation of the transgenic protein upon administration of an inhibitor, the mice had an innate, non-altered version of the gene that continued to be expressed (Applicants incorporate herein the specific comments on this point set forth at pages 5-7 of the Amendment filed November 9, 2009 in this application). Wang only suggests the

[1] To complete the record, Applicants are submitting herewith the Yamagata Declaration (October 27, 2009) and the Carpenter's Human Neuroanatomy publication, referenced in the November 9, 2009 Amendment, but not previously provided.

generation of knockin mice having the active form of the protein, and provides no studies or discussions whatsoever on mice expressing a kinase-*inactive* version of the protein alone. As to Elgersma, this publication was limited to studies of changes to the regulatory domain through mutation of residues 305 and 306. Elgersma provides no discussion whatsoever regarding the production of an animal having an inactive CaMKIIα without protein kinase activity, but retaining the other activities of the protein.

Even if the teachings of Hanson, Wang and Elgersma were combined, the CaMKIIα knockin mouse of the present invention could not be predictably generated because of the following reasons.

In higher eukaryotes, the gene control region, which includes the promoter and all of the regulatory sequences, varies among genes, both in composition and location. Different elements of the region may be dotted over great distances and sometimes the elements of one control region overlap with those of another (*see, e.g.,* p.400 of "Molecular Biology of The Cell, 4th edition" enclosed herewith). It is not unusual for part of the control region of one gene to be located within introns or exons of other genes, and the exact range and entire structure of many genes remain to be determined. Thus, genetic engineering to generate a knockin mouse, even if the manipulation of an exon of the target gene is limited and the exogenous DNA segment introduced into an intron is small, could result, at any time, in disruption of the gene control region of another gene that is important for early development, survival or breeding. Therefore, one skilled in the art recognizes that a combination of prior art does not simply lead to successful generation of a knockin mouse that is viable, healthy and has reasonable reproductive power.

In addition, successful generation of CaMKIIα knockout mice and Elgersma's knockin mice modifying Thr-305 and Thr-306 within the regulatory domain cannot predict successful generation of the knockin mouse of the present invention that modifies Lys-42 within the catalytic domain. This is because (1) the targeted exons and introns of the CaMKIIα gene, which consists of 18 exons and encompasses more than 50,000 nucleotide pairs, are completely different among these mutant animals, and (2) there is no information about whether these targeted sites may be localized within part of the gene control region of one or more important genes that are necessary for early development,

survival or breeding. Therefore, the combination of prior art, even with the additional knowledge from Hanson and Wang, does not teach successful generation of the inactive CaMKIIα knockin nonhuman animal of the present invention, which has a satisfactory birthrate, survival rate, and reproduction power as described in Example 6 of the specification.

Furthermore, Claim 2 denotes unexpected results of changes in neuronal activity observed in the inactive CaMKIIα knockin nonhuman animal of the present invention. As described in Example 7 and Figure 9 of the specification, no significant differences in cytochrome oxidase activities were found in the cerebral cortex (Cx) and corpus striatum (CPu) between the wild-type mouse and the homozygous knockin mouse (*note* that the term "CPu" in the specification is used as a synonym for "caudate-putamen" that excludes globus pallidus (*see* "Yamagata Declaration" and page 795, right column, second paragraph, lines 9-17, of "Carpenter's Human Neuroanatomy")). However, in the nucleus accumbens (Acc), the homozygous knockin mouse showed decreased cytochrome oxidase activity as compared to the wild-type mouse. This result indicates a decreased neuronal activity specifically in the nucleus accumbens of the homozygous knockin mouse of the present invention. See page 19, lines 18-27, of the specification. Such a characteristic is unexpected in light of the expression levels of CaMKIIα in the brain as described in Sutoo et al. (made of record on March 26, 2007). Sutoo states that CaMKIIα is highly expressed in the hippocampus, cerebral cortex, striatum (a synonym for "caudate-putamen"), nucleus accumbens, and amygdala. As the Examiner pointed out, CaMKIIα is well known to be involved in the regulation of neuronal activity. One skilled in the art would therefore expect that if a change in neuronal activity occurs in the inactivated knockin mice of the present invention, such a change should be detected prevalently in each of the above-mentioned brain areas that show a high expression level of CaMKIIα. Unexpectedly, however, the knockin mouse of the present invention showed decreased neuronal activity specifically in the nucleus accumbens, but not in the cerebral cortex nor in the caudate-putamen. The nucleus accumbens is known to be deeply involved in the regulation of emotional behavior and drug addiction. It has also been suggested that this brain area has a relationship with mental disease, including attention deficit hyperactivity disorder (ADHD) and schizophrenia. Accordingly, the knockin

animals and cells of the present invention would be useful tools for research into the pathophysiology, therapy and drug screening of such mental or psychiatric diseases, and drug addiction. See page 5, line 4-11, of the specification. Such a use for the present knockin animals and cells was completely unpredictable from the prior teachings of a functional role of CaMKIIα in the brain that emphasize a role for the protein primarily in learning and memory.

In addition, in light of the usage of the knockin animals and cells of the present invention as the above-mentioned disease models, the fact that the expression levels of the mutant CaMKIIα protein and CaMKIIβ protein are not affected in the knockin mice (as described in Example 5 and Figure 6) does have some importance. The phenotype of the knockin mice should be derived from the impaired protein kinase activity itself, and not from impairments of other functional activities of CaMKIIα. If the CaMKIIα protein level had been decreased, for example, as in the knockin mice of Elgersma, then the phenotypic expression of the mutation may be derived not only from impaired kinase activity, but also from reduced calmodulin-binding capacity, reduced formation of multimeric complexes that interact with other proteins, or compensatory, increased expression of related-proteins such as CaMKIIβ. The elucidation of the mechanisms of the pathophysiology and the selection of target points for therapeutics would thus become much too complicated.

Such functional aspects of the knockin mouse of the present invention cannot be predicted, even if the art of preparing knockin mice as disclosed in Elgersma or Wang is combined with the disclosure of Hanson and Sutoo.

Thus, in contrast to the Examiner's position, Applicants respectfully assert that the combination of the cited art does not teach the predictable generation of CaMKIIα mutants with the claimed activity. Further, as discussed above, the general knowledge in this field of endeavor teaches that the production of such animals would not have been predictable.

In view thereof, Applicants respectfully request reconsideration and withdrawal of this rejection.

II. Double Patenting

At page 5 of the office action, claims 20 and 23 are rejected as being substantial duplicates of claims 18 and 21, respectively, under 37 C.F.R. §1.75.

As discussed above, claims 20 and 23 are being canceled, thus making this rejection moot. In view thereof, reconsideration and withdrawal of this rejection is respectfully requested.

III. Conclusion

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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